Title

Hodgkin lymphoma post-transplant lymphoproliferative disorder: A comparative analysis of clinical characteristics, prognosis, and survival

Journal

American Journal of Hematology, 91(6)

ISSN

0361-8609

Authors

Rosenberg, Aaron S
Klein, Andreas K
Ruthazer, Robin
et al.

Publication Date

2016-06-01

DOI

10.1002/ajh.24346

Peer reviewed

HHS Public Access

Author manuscript

Am J Hematol. Author manuscript; available in PMC 2019 June 20.

Published in final edited form as:

Am J Hematol. 2016 June ; 91(6): 560–565. doi:10.1002/ajh.24346.

Hodgkin lymphoma post-transplant lymphoproliferative disorder: A comparative analysis of clinical characteristics, prognosis, and survival

Aaron S. Rosenberg[1,2,*], **Andreas K. Klein**[3,4], **Robin Ruthazer**[4,5], and **Andrew M. Evens**[3,4]

[1]University of California Davis School of Medicine, Sacramento, California

[2]Division of Hematology/Oncology, University of California Davis Medical Center, Sacramento, California

[3]Division of Hematology/Oncology, Tufts University Medical Center, Boston, MA

[4]Tufts Medical School, Boston, MA

[5]Tufts Clinical and Translational Science Institute, Boston, MA

Abstract

Hodgkin lymphoma post-transplant lymphoproliferative disorder (HL-PTLD) is an uncommon PTLD with unclear prognosis and differences between HL-PTLD and immunocompetent HL are not well defined. Patient characteristics were compared among 192 patients with HL-PTLD from the Scientific Registry of Transplant Recipients and 13,847 HL patients in SEER (HL-SEER). Overall survival (OS) and disease-specific survival (DSS) were compared after exact matching. Additionally, multivariable analyses were used to identify prognostic markers of survival and associations between treatment and survival. Median time from transplant to HL-PTLD diagnosis was 88 months. When compared with HL-SEER, patients with HL-PTLD were older (median age, 52 vs. 36 years, P=0.001), more likely male (73% vs. 54%, $P < 0.001$), Caucasian (81% vs. 70%, P=0.02), and had extranodal disease (42% vs. 3%, $P < 0.001$). Five-year OS for patients with HL-PTLD was 57% versus 80% for HL-SEER ($P < 0.001$); DSS was also inferior ($P < 0.001$). For patients with HL-PTLD, the use of any chemotherapy was associated with decreased hazard of death (HR=0.36, $P < 0.001$). Furthermore, patients who received no chemotherapy or nontraditional HL regimens had increased hazard of death (aHR=2.94, P=0.001 and 2.01, P=0.04) versus HL-specific chemotherapy regimens. In multivariable analysis, advanced age and elevated creatinine were associated with inferior OS (aHR=1.26/decade $P < 0.001$ and 1.64/0.1 mg/dL increase P=0.02). A prognostic score based on the number of these adverse factors (0, 1, 2) was associated with 10-year OS rates of 79%, 53%, and 11%, respectively ($P < 0.001$). Altogether, HL-PTLD patients have inferior survival when compared with HL-SEER. Furthermore, treatment

[*]Correspondence to: Aaron S. Rosenberg, University of California Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817. asrosenberg@ucdavis.edu.

Conflict of interest: Nothing to report

Disclosure

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

with HL-specific chemotherapy was associated with improved OS, whereas age and creatinine identified patients with markedly divergent survival.

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous group of diseases that arise after solid organ transplantation (SOT) [1]. Hodgkin lymphoma PTLD (HL-PTLD) is a relatively uncommon disease within the PTLD family [1–6]. The risk of developing HL after SOT, however, is significantly elevated when compared with the general population. In an analysis of SEER-Medicare, SOT recipients had 2.5 times the odds of developing HL versus controls [7], and a meta-analysis of European and Canadian registries estimated an incidence rate nearly four times greater than non-SOT recipients [8].

Disease outcomes and prognostication for patients who develop HL-PTLD are not well described. Most available data on the treatment of HL-PTLD have been reported in case reports and small series [9–22], and thus, there is minimal guidance when evaluating and treating this unique patient population. One registry study identified 60 patients with HL-PTLD in renal transplant recipients, all of whom were diagnosed prior to 2001 [6]. Interestingly, there were no deaths ascribed to malignancy, whereas a number of patients died due to infectious causes. The latter finding is consistent with reports of increased treatment-related mortality in monomorphic PTLD [23–26].

We designed a comprehensive cohort study of HL-PTLD from a large registry of SOT recipients to examine patient and disease characteristics, treatment modalities, survival rates, and to identify potential predictors of survival. In addition, to better characterize patient and disease-related factors as well as to put the HL-PTLD-related survival/outcomes into context, we compared patients with HL-PTLD to a matched cohort derived from SEER.

Patients and Methods

Data sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [27]. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. As of 1999, data on patients are collected by transplant centers at the time of SOT, at 6 months and then on the anniversary of the SOT. Data are entered in the online system UNet from prepopulated dropdown lists and as free text.

As a comparator group, patients with HL were identified in SEER (HL-SEER) [28], which provided demographic and survival information on all patients with cancer in geographic regions representative of the general U.S. population. The 2014 release of SEER 18 spans from 2000 to 2011, provided with a broad population base for comparison with the SRTR.

Patient identification

Patients were included in the HL-PTLD cohort if “Hodgkin’s disease” was recorded in the standardized diagnosis field or if “Hodgkin lymphoma” was entered in a diagnosis-related text field. Patients with HL-PTLD were excluded if they developed a solid tumor, except for noninvasive, nonmelanoma skin cancers, either preceding or following the HL-PTLD diagnosis. Patients identified only in transplant follow-up worksheets were also excluded as these patients did not have PTLD subtypes recorded. Patients with HL-SEER were identified using ICD-O-3 codes 9650, 9651–9655, 9661–9662, 9663–9667, and 9659, and those with prior malignancies were excluded.

Patient and treatment characteristics

A full description is supplied in the Appendix. Demographic characteristics were determined in the SRTR at time of listing for SOT. Performance status (PS), creatinine, and tumor characteristics were recorded at the transplant visit closest to the date of diagnosis with HL-PTLD. Treatment variables were standardized in a dependent fashion by two investigators (A. S. R. and A. K. K.); disagreements were reconciled by a third investigator (A. M. E.). Published combination chemotherapy regimens commonly used in the treatment of HL were considered Hodgkin-specific (Table AI).

Ascertainment of outcomes

The SRTR queries the Social Security Death Index, transplant centers, and organ procurement organizations to determine if patients have deceased. Patients were considered alive until the end of the study period (October 31, 2011) unless a date of death was entered. To account for this “presumed alive” approach when comparing outcomes in HL-PTLD and HL-SEER, a similar approach was used in SEER. The cause of death was based on death certificate data in SEER and ascertained by transplant centers in SRTR.

Matching

To compare outcomes between patient cohorts with HL-PTLD and HL-SEER, a matched cohort was compiled using exact matching on age rounded to the nearest whole year, sex, and year of diagnosis. Matching on race and extranodal status resulted in too many patients being excluded from the matched cohort. Therefore, these variables were excluded from the matching procedure, but accounted for in all multivariable models. One-to-many matching ratios were allowed to maximize sample size, with a range from 1:1 to 1:18. To account for this in the survival analyses, weights were assigned to individual subjects based on matching ratios.

Statistical analysis

Overall survival (OS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Disease-specific survival (DSS) was estimated by treating deaths not due to HL as censored events [29,30]. Cumulative incidence of HL-specific mortality was computed treating death due to other causes as a competing risk and compared using the methods proposed by Gray [31]. Cox proportional hazards models estimated the association between patient and treatment characteristics and OS. Multivariable analysis included

performance status and age and any variables with a univariate *P*-value<0.1. When comparing HL-SEER and HL-PTLD, stratified analyses accounting for the matching procedure and various matching ratios were performed. All missing data were assumed missing-at-random, and variables missing <33% were multiply imputed [32].

A prognostic model based on the variables identified as statistically significant in multivariable analysis was then derived. To determine cut points for continuous variables in a prognostic model, recursive partitioning trees were used [33]. A Coxproportional hazards model including the relevant dichotomized variables was fit, and the β-coefficients rounded to the nearest integer to determine a score for each variable. Individual patients were then assigned a score based on their baseline characteristics, and OS determined for each score, and differences tested using the log-rank test.

Sensitivity analyses

Sensitivity analyses were performed to evaluate analytic assumptions and to assess potential biases. Survival analyses excluded patients identified in text fields, using traditional censoring rather than “presumed alive” analyses and using complete case rather than multiply imputed data. Univariate analysis of creatinine and performance status limited to data collected within 30 days of diagnosis was performed. All analyses were performed using R version 3.1.1 (see Appendix for R-packages) [34] and RStudio (Boston, MA) [35].

Results

Patients

A total of 192 patients with HL-PTLD were identified in the SRTR (Table I). Time to HL-PTLD from SOT occurred at a median of 83 months (range, 0.2–239), and a small number of patients (*n*=17, 9%) had a prior PTLD diagnosis. The median age at diagnosis was 51 years (range, <0.5–78); the majority of patients were male (*n*=140, 73%) and Caucasian (*n*=156, 81%), which likely represents in part the underlying SOT population. Kidney was the most commonly transplant organ (52%) followed by liver (22%) and heart (21%), with the remaining patients receiving lung and pancreas transplants. Epstein-Barr virus (EBV) exposure, when recorded, was detected in 74% (*n*=70) of patients; and a relatively large proportion of patients with HL-PTLD (*n*=80, 42%) had extranodal disease at diagnosis. Ann Arbor stage and EBV status were missing in 134 (70%) and 98 (51%) of patients, respectively. Thus, neither were considered in survival analyses. When compared with patients with HL-PTLD, patients with HL-SEER (n=12,819; Table I) were less likely male (*n*=6,955, 54%) or Caucasian (*n*=8,990, 70%; *P*=0.001 and *P*<0.001, respectively), and the rate of extranodal disease was significantly (*n*=332, 3%) lower (*P*<0.001). After matching, 179 patients with HL-PTLD and 1,154 patients with HL-SEER were included for survival analyses (Table AII).

Treatment of HL-PTLD

Most patients underwent reduction of immunosuppression (RIS; *n*=130); 22 patients underwent RIS without other therapeutic intervention. Rituximab was administered to a

minority of patients (*n*=32), as was radiation therapy (XRT; *n*=37). No patients received rituximab alone (Fig. 1).

Chemotherapy was recorded for 145 patients (Fig. 1). Most patients received an HL-specific regimen (*n*=63, 43%), the remainder CHOP (*n*=35, 24%), and "other" nontraditional HL chemotherapy (*n*=47, 32%), whereas a small proportion received both HL-specific or CHOP and an "other" regimen (n=8, 6%; Fig. A1). The most common HL-specific regimen was ABVD or ABVD-like therapy (*n*=39, *n*=27%; Table AI). Patients who received CHOP or "other" regimens were older (median age, 55 and 45 years, respectively) than those who received HL-specific regimens (median age, 40 years; three-way ANOVA, *P*=0.06). Prediagnosis creatinine was modestly increased in patients receiving CHOP or "other" regimens (median 1.4 mg/dL) when compared with those who received HL-specific regimens (median 1.2 mg/dL; three-way ANOVA, *P*=0.18; Table AIII).

Survival

The median and 5-year OS for patients with HL-PTLD were 88 months (95% CI=58-not reached) and 57% (95% CI=50–66%), respectively. By comparison, in the matched HL-SEER cohort, median OS rate was not reached and 5-year OS was 78% (95% CI=76–81%; log-rank *P*<0.001; Fig. 2A). This translated into an adjusted hazard ratio (aHR) for death of 2.26 (1.65–2.09) after accounting for extranodal status and race as well as matching for age, sex, and year of diagnosis (Table AIV). Furthermore, DSS was similarly inferior for patients with HL-PTLD when compared with HL-SEER controls (5-year DSS 76% [95% CI=69–83%] vs. 85% [95% CI=83–87%], respectively, *P*<0.001; Fig. 2B).

As patients with HL-PTLD may be more likely to die of other causes than patients without prior SOT, disease-specific mortality may be overestimated in the HL-PTLD cohort, resulting in underestimation of DSS when compared with HL-SEER. To account for this, cumulative incidence curves of HL-specific mortality, treating other causes of death as a competing risk, were calculated. Patients with HL-PTLD had a 5-year HL-specific mortality rate of 23%, which compared with 13% for patients with HL-SEER (*P*<0.001). Furthermore, mortality due to other causes was also increased (5-year cumulative incidences of 20% vs. 6%, respectively, *P*<0.001; Fig. A2).

In univariate analyses for factors prognostic of survival, age at diagnosis, receipt of a heart transplant, and elevated serum creatinine were associated with shorter survival. In the multivariable model, which included these variables and performance status, only age and creatinine remained significant with aHRs of 1.26/decade (95% CI=1.11–1.42) and 1.64/0.1 mg/dL increase in creatinine (95% CI=1.12–2.39; Table II). In a multivariable model of DSS, both advanced age and increased serum creatinine were similarly associated with worse outcomes: aHR 1.29/decade (95% CI=1.08–1.53) and 1.54/0.1 mg/dL increase in creatinine (95% CI=1.09–2.16). To determine if the effect of creatinine on survival differed in patients with kidney transplant versus other transplanted organs, the interaction between kidney transplant and serum creatinine was tested and found to be statistically significant (*P*=0.04). The aHR for serum creatinine among renal transplant recipients was 2.83 when compared with 1.61 for other SOT types (Table AV). However, in a multivariable model including age, creatinine, performance status, and kidney transplant, and the interaction

term, neither kidney transplant nor the interaction term retained statistical significance (Table AVI).

The use of chemotherapy was associated with a significant decrease in the hazard of death (HR=0.36 [95% CI=0.23–0.57]). The type of chemotherapeutic regimen was also associated with survival; median OS of patients who received an HL-specific regimen was not reached when compared with 15, 93, and 88 months for patients who had received no chemotherapy, CHOP, and nontraditional chemotherapeutic regimens, respectively ($P<0.001$). The DSS for patients receiving HL-specific regimens was superior to those who received CHOP, nontraditional, and no chemotherapy (5-year DSS 91%, 68%, 72%, and 53%, respectively, $P<0.001$; Fig. 2D). Taking into account competing risks, the 5-year cumulative incidence of HL-related mortality was only 8% in patients receiving HL-specific regimens when compared with 20, 28, and 41% in those receiving CHOP, nontraditional, and no chemotherapy, respectively ($P<0.001$; Fig. A3A). Interestingly, the cumulative incidence of mortality due to other causes was not different in the four treatment groups ($P=0.33$; Fig. A3B).

When accounting for differences in baseline characteristics, OS for patients who received CHOP was no longer statistically significantly inferior to HL-specific regimens (aHR=1.62, 95% CI=0.78–3.37), whereas OS for patients who received nontraditional regimens or no chemotherapy remained significantly inferior (aHR [95% CI]=2.01 [1.04–2.89] and 2.94 [1.56–5.55], respectively). By comparison, the use of HL-specific regimens was associated with superior DSS when compared with CHOP, nontraditional chemotherapy regimens, and no chemotherapy in the multivariable models (Table AVII). Mortality was not affected by the use of radiation therapy, reduced immunosuppression, or by rituximab (data not shown).

Prognostic score

To create a prognostic score for survival, the two baseline characteristics found to be significant in the multivariable model (i.e., age at diagnosis and serum creatinine) were dichotomized at 55 years and 1.20, respectively. A Cox proportional hazards model was run (Table AVIII) on the multiply imputed data set, and the β-coefficients rounded to the nearest integer to give a point value: both age ≥55 and creatinine ≥1.20 gave 1 point. Patients were then assigned a total score based on age and creatinine at diagnosis. Outcomes were significantly different in the three groups with 10-year OS rates of 79% (95% CI=62–100%) in the low-risk group, versus 53% (41–68%) in the intermediate, and 11% (2–51%) in the high-risk group ($P<0.001$; Fig. 2E). The prognostic score performed similarly regarding DSS, with 10-year DSS rates of 91% (81–100%), 77% (68–88%), and 42% (27–65%) in the three groups, respectively (log-rank $P<0.001$).

Sensitivity analysis

Several sensitivity analyses were performed to assess for potential biases, various assumptions, and analytic techniques that may have introduced into the study. None of these analyses yielded results that differed substantively when compared with the main analyses presented above (Tables AIX–AXII).

Discussion

To the best of our knowledge, this is the largest study of HL-PTLD reported to date. We identified that demographics of patients who develop HL-PTLD differ significantly from those who develop HL in the general population; patients with HL-PTLD tend to be older, more likely male and Caucasian and have extranodal disease. When these and other characteristics were controlled, both OS and DSS of HL-PTLD were shorter versus patients with HL-SEER. Indeed, although HL-PTLD is curable, with a significant proportion of patients achieving long-term survival, in older patients and those with elevated creatinine, survival times are limited. Dramatic differences in survival were noted between younger patients with normal creatinine when compared with those with a creatinine ≥1.2, age ≥55 years, or both, and patients receiving Hodgkin-specific chemotherapy regimens had significantly improved survival.

HL-PTLD is an uncommon disease, accounting for approximately 3–8% of PTLD cases in various single-institution series and registries [2–6,36,37]. However, when compared with the general population, there is an increased incidence of HL occurring after SOT, with a meta-analysis of epidemiologic studies reporting a standardized incidence ratio of 3.89 (95% CI=2.42–6.26) [8], and an analysis of SEER-Medicare reported an odds ratio of 2.53 (95% CI=1.01–6.35) [7]. Little is known about the survival of HL-PTLD; however, in one analysis of the US Renal Data Service, 60 patients with HL-PTLD were identified and 16 (27%) died, although none died of HL.

Data on the treatment of HL-PTLD is even more scant and has been primarily restricted to case reports and case series totaling 39 patients [10–21,38]. Chemotherapy has been commonly administered, although follow-up varied greatly across reports. Toxicity has been infrequently reported, although three patients reported in the earliest series suffered infectious complications after receiving ABVP, ABVD, and COPP/ABV [10,11,38], as did two additional patients treated on pediatric HL protocols [18], leading to concerns of the tolerability of standard Hodgkin-specific treatment regimens in the post-SOT population [9]. Survival was not routinely reported, but ranged from 2 to 123 months.

In the current analysis, the use of combination chemotherapy, and particularly those regimens designed to treat HL, was associated with significant improvements in OS and DSS. Interestingly, the use of HL-specific chemotherapy regimens was associated with decreased HL-specific mortality, whereas the rates of death due to other causes were no different than for patients receiving no chemotherapy, nontraditional chemotherapy, or CHOP. This suggests that toxicity is not different among various treatment strategies. Importantly, as with HL in the general population, DSS curves reach a plateau around 5 years, indicating that a large proportion of these patients are cured with appropriate therapy.

A strength of this observational study of registry data is the robust sample that is likely representative, and thus generalizable, to the population of patients with HL-PTLD. However, several limitations should be acknowledged. This registry does not specifically collect data regarding the timing of treatment, relapse, or changes in therapy. Data on stage and tumor EBV status are frequently missing, whereas other data, such as tumor bulk, serum

lactate dehydrogenase, and erythrocyte sedimentation rate are not collected. Comparisons with HL-SEER are made more difficult as stage could not be accounted for; however, the matching algorithm allowed us to keep all patients who had a match, thus the HL-SEER patient population is very general, and likely includes patients with a variety of stages for each match. This is unlikely to systematically bias the survival estimates toward or away from the null hypothesis. Moreover, easily obtainable clinical data at the time of diagnosis, namely, age and serum creatinine, were highly correlated with survival. It was surprising to find that Karnofsky performance status was not associated with outcomes; however, very few patients had poor performance status, and thus, this finding is somewhat limited. Although data on serum creatinine were missing in one-third of the patients, multiple imputations allowed for patients with missing data to be retained in multivariable models, and the association between elevated creatinine and shortened survival was stable across multiple sensitivity analyses.

Treatment data have been lacking in this disorder, and the current study offers the first detailed evaluation of treatment patterns and outcomes in a large number of HL-PTLD patients. Treatment data are collected during yearly follow-ups with patients with SOT, and thus, the timing of serial treatments cannot be accounted for; however, it appeared that patients who received HL-specific combination chemotherapy had improved survival times.

In conclusion, HL-PTLD is a serious complication of SOT that is associated with a higher mortality rate than HL in the non-SOT population. In particular, older patients with elevated creatinine are at the highest risk of death. Treatment with HL-specific regimens appears to be the most effective, although CHOP, as in other forms of monomorphic PTLD, may also be considered. Continued biologic and clinical examination of this interesting and uncommon subtype of PTLD is needed to potentially improve outcomes for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The current study was initiated at the Tufts Medical Center while the corresponding author was employed there. It was deemed nonhuman research by the Tufts Medical Center IRB because it relies solely on de-identified registry data.

Contract grant sponsor: NIH; Contract grant numbers: UL1 TR001064, T32HS000060.

Contract grant sponsor: NIH/NCI; Contract grant number: R01CA164311.

References

1. Swerdlow S, Webber S, Chadburn A, Ferry J Post-transplant lymphoproliferative disorders. The 2008 WHO Classification of Tumours for Haematopoietic adn Lymphoid Tissues In: Swerdlow SH, Campo D, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. eds. WHO Classification of Tumours for Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer (IARC); 2008 pp 343–349.

2. Caillard S, Lamy FX, Quelen C, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant 2012;12:682–693. [PubMed: 22226336]

3. Morton M, Coupes B, Roberts SA, et al. Epidemiology of posttransplantation lymphoproliferative disorder in adult renal transplant recipients. Transplantation 2013;95:470–478. [PubMed: 23222821]

4. Piselli P, Serraino D, Segoloni GP, et al. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. Eur J Cancer 2013;49:336–344. [PubMed: 23062667]

5. Quinlan S, Pfeiffer R. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am J Hematol 2011;86:206–209. [PubMed: 21264909]

6. Caillard S, Agodoa LY, Bohen EM, Abbott KC. Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: characteristics, risk factors and prognosis. Transplantation 2006;81:888–895. [PubMed: 16570013]

7. Quinlan SC, Morton LM, Pfeiffer RM, et al. Increased risk for lymphoid and myeloid neoplasms in elderly solid-organ transplant recipients. Cancer Epidemiol Biomarkers Prev 2010; 19:1229–1237. [PubMed: 20406959]

8. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:59–67. [PubMed: 17617273]

9. Zimmermann H, Trappe RU. EBV and posttransplantation lymphoproliferative disease: what to do? Hematol. Am. Soc. Hematol. Educ. Program 2013;2013:95–102.

10. Bierman P, Vose J, Langnas A, et al. Hodgkin's disease following solid organ transplantation. Ann. Oncol. 1996;7:265–270. [PubMed: 8740790]

11. Garnier J, Lebranchu Y, Dantal J, et al. Hodgkin's disease after transplantation. Transplantation 1996;61:71–76. [PubMed: 8560577]

12. Zambelli A, Lilleri D, Baldanti F, et al. Hodgkin's disease as unusual presentation of posttransplant lymphoproliferative disorder after autologous hematopoietic cell transplantation for malignant glioma. BMC Cancer 2005;5:109. [PubMed: 16117828]

13. Pitman SD, Huang Q, Zuppan CW, et al. Hodgkin lymphoma-like posttransplant lymphoproliferative disorder (HL-like PTLD) simulates monomorphic B-cell PTLD both clinically and pathologically. Am J Surg Pathol 2006;30:470–476. [PubMed: 16625093]

14. Schlieper G, Kurschat C, Donner A, et al. Hodgkin disease-like posttransplantation lymphoproliferative disorder of donor origin in a renal allograft recipient. Am J Kidney Dis 2006;47: e37–e41. [PubMed: 16490613]

15. Flanagan KH, Brennan DC. EBV-associated recurrent Hodgkin's disease after renal transplantation. Transpl Int 2006;19:338–341. [PubMed: 16573551]

16. Gheorghe G, Albano EA, Porter CC, et al. Posttransplant Hodgkin lymphoma preceded by polymorphic posttransplant lymphoproliferative disorder: report of a pediatric case and review of the literature. J Pediatr Hematol Oncol 2007; 29:112–116. [PubMed: 17279008]

17. Choi JH, Ahn MJ, Oh YH, et al. Epstein-Barr virus-associated Hodgkin's disease following renal transplantation. Korean J Intern Med 2006;21:46. [PubMed: 16646565]

18. Rohr JC, Wagner HJ, Lauten M, et al. Differentiation of EBV-induced post-transplant Hodgkin lymphoma from Hodgkin-like post-transplant lymphoproliferative disease. Pediatr Transplant 2008;12:426–431. [PubMed: 18466428]

19. Krishnamurthy S, Hassan A, Frater JL, et al. Pathologic and clinical features of Hodgkin lymphoma-like posttransplant lymphoproliferative disease. Int J Surg Pathol 2010;18:278–285. [PubMed: 19578050]

20. Basso S, Zecca M, Calafiore L, et al. Successful treatment of a classic Hodgkin lymphoma-type post-transplant lymphoproliferative disorder with tailored chemotherapy and Epstein-Barr virus-specific cytotoxic T lymphocytes in a pediatric heart transplant recipient. Pediatr Transplant 2013;17:E168–E173. [PubMed: 23992468]

21. Ranganathan S, Webber S, Ahuja S, Jaffe R. Hodgkin-like posttransplant lymphoproliferative disorder in children: does it differ from posttransplant Hodgkin lymphoma? Pediatr Dev Pathol 2004;7:348–360. [PubMed: 14564542]
22. Ranganathan S, Jaffe R. Is there a difference between Hodgkin's disease and a Hodgkin's-like post-transplant lymphoproliferative disorder, and why should that be of any interest? Pediatr Dev Pathol 2004;7:348–360. [PubMed: 14564542]
23. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 2006;6:569–576. [PubMed: 16468968]
24. Choquet S, Trappe R, Leblond V. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders following solid organ transplantation. Haematologica 2007;92:273–274. [PubMed: 17296588]
25. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196–206. [PubMed: 22173060]
26. Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol 2010;28:1038–1046. [PubMed: 20085936]
27. Procurement Organ and Network Transplantation (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2012 Annual Data Report. Am J Transplant 2013;14:5–192. [PubMed: 24165437]
28. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973–2011), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.
29. Howlader N, Ries LAG, Mariotto AB, et al. Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst 2010;102:1584–1598. [PubMed: 20937991]
30. Pintilie M. Analysing and interpreting competing risk data. Stat Med 2007;26:1360–1367. [PubMed: 16900575]
31. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141–1154.
32. Steyerberg E Clinical Prediction Models. Springer Science+Business Media; New York, NY, 2009.
33. Breiman L, Friedman J, Stone CJ, Olshen R. Classification and Regression Trees Wadsworth International; CRC Press LLC, Boca Raton, Florida, 1984.
34. R Core Team. R: A language and environment for statistical computing. Vienna, Austria, 2013.
35. RStudio Team. (www.rstudio.com) RStudio: Integrated development environment for R Boston, MA, 2012.
36. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005;80:1233–1243. [PubMed: 16314791]
37. Caillard S, Porcher R, Provot F, et al. Post-transplantation lymphoproliferative disorder after kidney transplantation: report of a nationwide French registry and the development of a new prognostic score. J Clin Oncol 2013;31:1302–1309. [PubMed: 23423742]
38. Dharnidharka VR, Douglas VK, Hunger SP, Fennell RS. Hodgkin's lymphoma after posttransplant lymphoproliferative disease in a renal transplant recipient. Pediatr Transplant 2004;8: 87–90. [PubMed: 15009846]

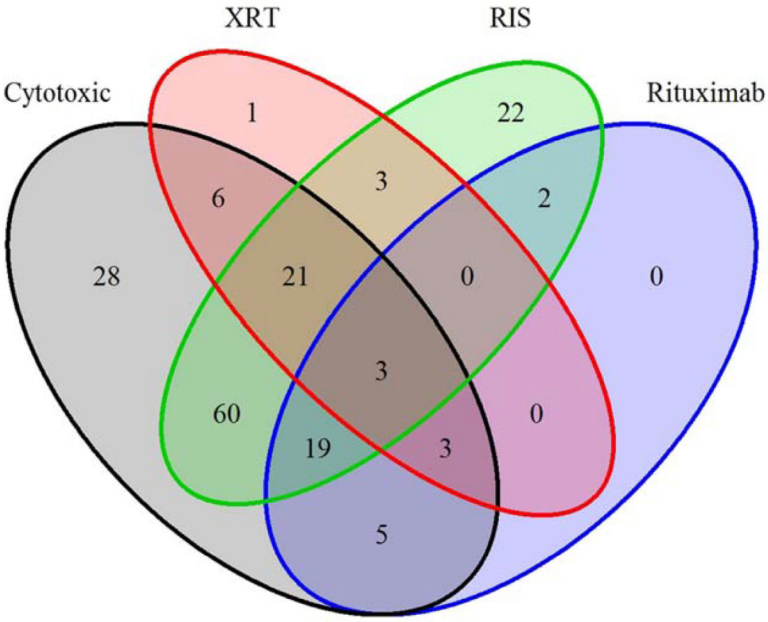

Figure 1.

Treatment of HL-PTLD Venn diagram. Treatment was recorded in 173 patients with HL-PTLD. Chemotherapy was used in 145 (84%) patients, a majority of patients (103, 60%) also underwent reduction in immunosuppression. Radiation therapy was used in the minority of patients (37, 22%), and only four patients received radiation without chemotherapy. Immunosuppression was reduced in 130 (76%) patients, and in 22 (13%) patients, this was the only recorded therapeutic intervention. Abbreviations: RIS, reduction of immunosuppression; XRT, radiation therapy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

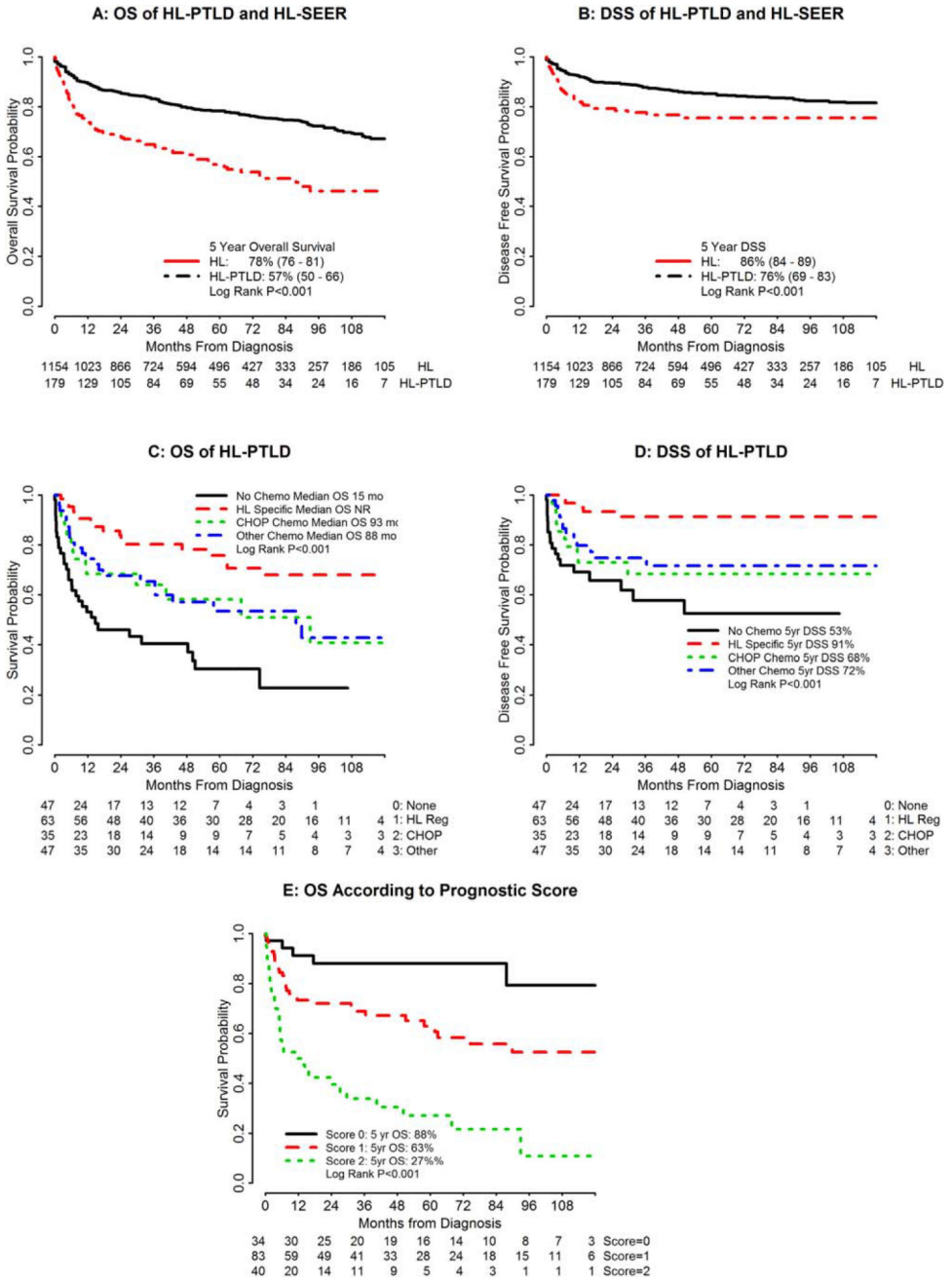

Figure 2.

Overall and disease-specific survival of patients with HL-PTLD and HL-SEER and of patients with HL-PTLD according to chemotherapy received and by prognostic score. In the cohorts of HL-PTLD and HL-SEER matched on age at diagnosis, sex, and year of diagnosis, (A) overall survival of HL-PTLD is significantly decreased when compared with HL-SEER, with 5-year estimates of 57% and 78%, respectively (P<0.001). In the same cohorts, (B) disease-specific survival is similarly inferior in HL-PTLD when compared with HL-SEER: 5-year estimates are 76% and 86%, respectively (P<0.001). Patients with HL-PTLD who were treated with chemotherapy survived significantly longer than those who did not, and

the chemotherapeutic regimen used affected overall survival (C) and disease-specific survival (D). When the prognostic score (one point each for age ≥55 years and serum creatinine ≥1.2) was applied to patients with HL-PTLD (E), those with a score of 0 lived significantly longer than those with a score of 1 or 2. The hazards of death in those with a score of 1 or 2 when compared with a score of 0 are 3.1 (1.2–7.9) and 8.7 (3.4–22.6), respectively. Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DSS, disease-specific survival; HL-PTLD, Hodgkin lymphoma post-transplant lymphoproliferative disorder; HL-SEER, Hodgkin lymphoma controls derived from SEER; HL-specific: chemotherapy regimen specifically targeting Hodgkin lymphoma; OS, overall survival. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I.

Patient Characteristics

Variable	HL-PTLD (*n*=192)	HL-SEER (2000–2011)[a] (*n*=12,819)
Male	140 (73%)	6,955 (54%)
Age in years (range)	51 (0–78)	36 (2–96)
Race		
Caucasian (non-Hispanic white)	156 (81%)	8,990 (70%)
African American	15 (8%)	1,495 (12%)
Hispanic	17 (9%)	1,833 (14%)
American Indian/Alaskan	1 (1%)	33 (<1%)
Asian	3 (2%)	353 (3%)
Other/unknown	-	115 (1%)
SOT type		
Heart	40 (21%)	NA
Kidney	100 (52%)	NA
Liver	42 (22%)	NA
Lung	8 (4%)	NA
Pancreas	2 (1%)	NA
Prior PTLD	17 (9%)	NA
Prior post-SOT skin cancer[b]	11 (6%)	NA
Months from SOT to PTLD (range)	83 (0.2–239)	NA
Stage		
I	6 (3%)	2,250 (18%)
II	16 (8%)	5,127 (40%)
III	19 (10%)	2,500 (20%)
IV	17 (9%)	2,184 (17%)
Unknown/missing	134 (70%)	758 (6%)
Nodal	120 (63%)	12,487 (97%)
Unknown/missing	31 (16%)	
Extranodal	80 (42%)	332 (3%)
HBV at SOT	2 (1%)	NA
NA	24 (13%)	NA
HCV at SOT	13 (7%)	NA
NA	51 (27%)	NA
Creatinine (median, range)	1.3 (0.2–5.5)	NA
NA	60 (31%)	NA
Karnofsky performance status		
80–100	106 (55%)	NA
60–70	11 (6%)	NA
10–50	5 (3%)	NA
NA	70 (36%)	NA

All continuous variables are expressed as medians with interquartile ranges.

[a] Only includes patients with age recorded, no prior malignancies, and had survival time recorded.

[b] Noninvasive, nonmelanoma.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HL-PTLD, Hodgkin lymphoma post-transplant lymphoproliferative disorder; HL-SEER, Hodgkin lymphoma controls derived from SEER; NA, not available; SOT, solid organ transplant.

TABLE II.

Patient Characteristics and Association with Overall Survival.

	Pooled over multiply imputed data[a]				Complete case			
	Univariate		Multivariable		Univariate		Multivariable	
Variable	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***	**HR (95% CI)**	***P*-value**	**aHR (95% CI)**	***P***
Male	1.08 (0.66–1.75)	0.76			1.08 (0.66–1.75)	0.76		
Age (in decades)	1.30 (1.15–1.45)	<0.001	1.26 (1.11–1.42)	0.000	1.30 (1.15–1.45)	<0.001	1.31 (1.07–1.61)	0.01
Race	R^2=0.014	*P*=0.62			R^2=0.014	*P*=0.62		
Caucasian	1	Reference			1	Reference		
African American	0.77 (0.45–1.31)	0.33			0.77 (0.45–1.31)	0.33		
Hispanic	1.29 (0.78–2.14)	0.32			1.29 (0.78–2.14)	0.32		
Native American/Alaskan	1.98 (0.27–14.23)	0.50			1.98 (0.27–14.23)	0.50		
Asian	0.81 (0.26–2.57)	0.73			0.81 (0.26–2.57)	0.73		
Cardiac allograft versus all others	1.63 (1.02–2.61)	0.04	1.42 (0.81–0.48)	0.21	1.63 (1.02–2.61)	0.04	NA[b]	
Prior PTLD	1.11 (0.56–2.22)	0.77			1.11 (0.56–2.22)	0.77		
Years to PTLD	1.04 (0.99–1.09)	0.12			1.04 (0.99–1.09)	0.12		
Nodal	0.85 (0.50–1.45)	0.56			0.85 (0.50–1.45)	0.56		
Extranodal	1.05 (0.69–1.61)	0.82			1.05 (0.69–1.61)	0.82		
HBV at SOT[a]	1.10 (0.32–3.74)	0.87			1.43 (0.20–10.3)	0.73		
HCV at SOT[a]	1.20 (0.61–2.39)	0.58			1.26 (0.50–3.16)	0.63		
Creatinine (per 0.1 mg/dL change)[a]	1.81 (1.30–2.51)	0.002	1.64 (1.12–2.39)	0.02	1.88 (1.45–2.45)	<0.001	1.54 (1.06–2.22)	0.02
Poor KPS (10–70)[a]	1.48 (0.77–2.84)	0.23	1.19 (0.68–2.09)	0.54	2.06 (1.0–4.24)	0.05	1.93 (0.72–5.20)	0.19
Year of diagnosis	1.00 (0.93–1.07)	0.90			1.00 (0.93–1.07)	0.90		

Multiple imputations were performed using 350 iterations on five data sets.

[a]Missing data multiply imputed for HBV, HCV, creatinine, and performance status.

[b]36/40 patients with cardiac allografts were missing serum creatinine.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; KPS, Karnofsky performance status; PTLD, post-transplant lymphoproliferative disorder.